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Recanalization of occluded large arteries with broadened therapeutic window for acute cerebral infarction

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ABSTRACT

Objective: To investigate the safety and efficacy of recanalization with a broadened therapeutic window for acute occlusion of large cerebral arteries.
Methods: We assessed 38 patients who underwent the hyper-selective intra-arterial administration of low-dose urokinase, along with mechanical thrombus disruption or mechanical thrombus disruption recanalization (34 stents in 33 patients) of occluded vessels, 20 with onset time-to-treatment (OTT) >6 h (observation group; mean OTT, 20.10 ± 15.67 h) and 18 with OTT ≤6 h (control group). NIHSS scores, mRS scores (≤2) at 3 months, recanalization rates, severe cerebral infarctions on CT, and symptomatic hemorrhagic conversions after surgery were compared.
Results: Postoperative recanalization rates were 100% in both groups, and other results were equivalent.
Conclusions: Recanalization at longer OTT was safe and effective with acute occlusions of large cerebral arteries. Time to recanalization could be safely prolonged for up to 20 h in these patients.

1. Introduction

The development of neurointerventional procedures has led to enhanced restoration of timely blood flow in occluded cerebral arteries. Intravenous and intra-arterial thrombolysis are important for the timely restoration of cerebral blood flow. Current Chinese guidelines for stroke patients recommend time windows for intravenous and intra-arterial thrombolysis of 4.5 and 6 h, respectively. Even in developed countries, however, few patients are transferred to the hospital within these time windows. The median pre-hospital delay time has ranged from 5.4 to 7.9 h, with <30% transferred within 3 h and <53% within 6 h [1,2]. In addition, the recanalization rate was only about 50% in patients who underwent intravenous thrombolysis and 66% in those who underwent intra-arterial thrombolysis [3,4]. The development of various mechanical thrombectomy devices has improved the recanalization rate in patients with cerebral artery occlusions caused by white thrombosis, resulting in recanalization rates of 81.6–88% [5,6]. To the best of our knowledge, the therapeutic time window for these systems has been reported to be less than 8 h, but many patients with cerebral large artery occlusions cannot arrive at a hospital in a condition suitable for removing the thrombus within 8 h after stroke onset.

Although the collateral circulation can supply a small amount of blood to distal occluded arteries, most occluded vessels in the trunk will have collapsed, making the cerebral blood supply in this region insufficient [7,8]. Restoration of blood flow cannot only help in the functional recovery of brain tissue, but can also prevent the recrudescence of low perfusion cerebral infarction. We have therefore assessed the optimal time for interventional recanalization in patients with symptomatic acute cerebral artery occlusions.

2. Materials and methods

2.1. General information

We assessed 38 of 863 patients with cerebral infarction who were admitted to our department and underwent 4-vessel cerebral Digital Subtraction Angiography (DSA) from August 2008 to February 2012. Patients were included if they were <85 years old; had arrived at our hospital within 72 h of stroke onset; had sudden-onset severe hemiparalysis or disturbance of consciousness and a National Institutes of Health Stroke Scale (NIHSS) score ≥8 [9]; and presented with occlusion of a large cerebral blood vessel (including the carotid artery, basilar artery, or trunk of the middle cerebral

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artery) on cerebral DSA corresponding to the suspected ischemic territory. All patients underwent CT scanning at admission and were initially treated with a 4000 U bolus of heparin. Patients were excluded if they had another serious neurological disabling disease or a critical systemic condition of the heart, liver or kidneys; had undergone surgery within 3 months; or had a known bleeding tendency. Patients were also excluded if CT scanning showed evidence of any intracranial hemorrhage or early and obvious evidence of size-matched low density foci related to this attack, or if families of patients refused cerebral angiography and/or recanalization operation. The study protocol was approved by our institutional Ethics Committee, and informed consent was obtained from family members of each patient.

Patients were divided into two groups based on onset time-to-treatment (OTT). The 18 patients in the control group (15 men, 3 women; mean age 56.79 ± 14.16 years; range 44–83 years) had an OTT ≤6 h (mean, 4.0 ± 0.86 h; range, 3–6 h). The 20 patients in the observation group (17 men, 3 women; mean age, 54.28 ± 11.27 years; range 40–73 years) had an OTT >6 h (mean, 20.10 ± 15.67 h; range, 6.5–66 h).

All patients underwent cerebral angiography to identify the location of the occluded artery and the collateral circulation at the lesion site. Complete communicating arteries, sufficient compensation, or an old cerebral infarction corresponding to the occluded vessel were considered contraindications for recanalization. Recanalization was indicated if (1) the proximal part of the offending vessel was occluded and the blood flow in the compensated distal vessel was poor, or (2) a brain CT scan did not reveal a related cerebral infarct or a small sized cerebral infarct (<10% occluded vessel territory) related to this attack, especially a size mismatched cerebral watershed infarction. Of the 18 patients in the control group, 3 had basilar artery occlusion, 6 had occlusions at the origin of the internal carotid artery (ICA); 5 had occlusions of other segments of the ICA, and 4 had cerebral middle artery (MCA) occlusions. In the observation group, 1 patient had a basilar artery occlusion; 5 had occlusions at the origin of the ICA; 6 had occlusions of other segments of the ICA, and 8 had occlusions of the MCA.

2.2. Recanalization methods

A 6/8-F guide-catheter was placed in the proximal occluded vessel and crossed slowly with a microcatheter under the guidance of a microguidewire. Using microcatheter angiography, the length of the occluded segment and the conditions of the occluded vessel were determined. If the distal end of the occluded vessel showed patency on DSA, a suitable stent, such as an ev3 Stent (ev3 Endovascular, Plymouth, MN, USA), an Apollo Stent (MicroPort, Shanghai, China) or a Wingspan Stent (Boston Scientific, USA), was inserted into the occluded site. Four patients received a continuous hyper-selective intra-arterial infusion of 200,000–300,000 U (10,000 U/min) urokinase (Nanjing Nanda Pharmaceutical Corporation, China, Approval code: H10920040) through the microcatheter at the initial stage. Two patients, one each with an occlusion in the MCA and ICA, underwent thrombus disruption using a balloon catheter. Three patients, 2 with occlusion of the MCA and one with a lymphoma occlusion of the ICA, underwent thrombus entrapment with a Solitaire AB stent (ev3 Endovascular, Plymouth, MN, USA). The final 5 patients did not undergo stent implantation. Thus all 18 patients in the control group, and 15 of 20 in the observation group, 1 with 2 stents, underwent stenting.

Immediately following surgery, all patients underwent repeat angiography to determine the extent of recanalization and brain CT to determine the presence or absence of an intracerebral hemorrhage. The end points of the operation were defined as complete recanalization of the occluded vessel, an operation time >3 h, and patient improvement or hemorrhagic tendency.

2.3. Perioperative medication

Prior to surgery, all patients received oral clopidogrel 450 mg [Sanofi-Aventis (Hangzhou) Pharmaceutical Co., Ltd., China, Approval code: J20080090], enteric-coated aspirin 300 mg (Bayer Company, Germany, Approval code: J20080078), and intravenous heparin (67 U/kg), followed by a half dose of heparin every hour during surgery. Immediately following recanalization, patients received an intraductal bolus injection of edaravone 30 mg (Jida Pharmaceutical Co., Ltd., Kunming, China, Approval code: H20080495) plus 30 ml heparin liquid. All patients received edaravone 30 mg IV twice daily for 3–7 days postoperatively, with blood pressure strictly controlled at 10–20% below preoperative levels. Patients continued to receive oral aspirin 300 mg/d, clopidogrel 75 mg/d, and atorvastatin calcium 20–40 mg/d (Pfizer Pharmaceutical Company, USA, Approval code: J20070061) for 3 months postoperatively. Other drugs given during surgery included mannitol, atropine, and dopamine, depending on patient requirement.

2.4. Evaluation of occluded vessel recanalization

Angiographic recanalization was classified according to the Thrombolysis in Myocardial Infarction (TIMI) grading system.

2.5. Continuous observation index

NIHSS was determined before surgery, immediately after surgery, and after 24 h, 7 and 14 days and 3 months, by two professional staff members blinded to the treatment protocols. Clinical outcomes 3 months after surgery were evaluated using the Modified Rankin Scale (mRS), with good outcomes defined as mRS scores ≤2. All patients underwent brain CT examinations preoperatively and immediately after surgery, with 35, 33, and 33 patients undergoing brain CT after 24 h, 7 days and 14 days, respectively.

2.6. Symptomatic intracerebral hemorrhagic conversion

Symptomatic intracerebral hemorrhagic conversion (sICH) was defined as secondary bleeding, a ≥4 point increase in NIHSS, or death within 7 days.

2.7. Definition of severe cerebral infarction on brain CT

Severe cerebral infarction was defined as a cerebral infarction threatening the life of the patient or of a size large enough on CT to involve two lobes of the cerebral hemisphere within 7 days.

2.8. Duration of surgery

Duration of surgery was defined the time from the beginning of operative disinfection to the end of the operation. Mean duration was 2.18 ± 0.67 h in the control group and 2.00 ± 0.48 h in the observation group.

2.9. Statistical methods

All data were analyzed using SPSS 11.0 software. Categorical data were expressed as composition ratio and compared using Fisher's exact test; and numerical data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared by Student's *t*-tests and nonparametric tests. Significance was set at $P < 0.05$.